

Management of asymptomatic bacteriuria in children

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Abstract

Question I am aware of how common pediatric urinary tract infection (UTI) is, and of the potential long-term sequelae if left untreated. Therefore, in our practice we treat every child who presents with symptomatic UTI with antibiotics. However, should the same practice be applied to children with bacteriuria that is asymptomatic?

Answer Historically, asymptomatic bacteriuria (ABU) was treated with antibiotics in all populations, including in children. However, more recent evidence has shown no benefit and often harm associated with the use of antibiotics to treat pediatric ABU. Some studies suggest that owing to the different microbiology associated with ABU it should not be considered in the spectrum of UTI. These children should not be treated with antibiotics unless they have received a renal transplant or have undergone invasive urologic procedures.

Urinary tract infection (UTI) is a source of fever in 7% of sick neonates, 13.6% of febrile infants younger than age 1, and 10% of children seen in emergency departments.^{1,2} It is expected that 7% of girls and 2% of boys will experience at least 1 episode of UTI before the age of 6.³ Urinary tract infection is more common in girls, with the exception of uncircumcised boys younger than age 5.⁴ The presentation of UTI in the pediatric population varies greatly, thus making the diagnosis difficult.

The current standard of care is antibiotic treatment of all children presenting with UTI owing to the risk of renal impairment and hypertension. The prevalence of substantial renal damage, with reduced glomerular filtration rate or abnormalities revealed on intravenous urography, has been reported to be 0.4% in febrile children with UTI who otherwise have normal renal anatomy, and up to 56% in children aged 1 to 12 who have known urologic abnormalities, such as severe bilateral vesicoureteral reflux.^{5,6} Furthermore, between 2% and 6% of adults with hypertension have a history of febrile UTI.⁶ Finally, up to 15% of children with a first UTI are showing evidence of renal scarring (as measured by dimercaptosuccinic acid scan), which was linked to the development of hypertension.⁷

Asymptomatic bacteriuria

Asymptomatic bacteriuria (ABU) is the finding of positive cultures ($\geq 10^5$ colony-forming units of bacteria per mL of urine) of the same uropathogen from 2 consecutive urine samples, in the absence of urinary symptoms. The prevalence of ABU is estimated to be less than 1% in full-term infants, 3% in school-aged children, and 1% in older children.^{8,9}

Similar to symptomatic UTI, ABU generally involves Gram-negative bacteria, such as *Escherichia coli*; however,

the ABU-related bacterial strains express fewer virulence factors than those bacterial strains involved in febrile UTI, and have been found to have different genes that encode for the production of fimbriae, which are important for the ability of *E. coli* to ascend in the urinary tract.¹⁰ Furthermore, in vitro studies of a strain of *E. coli* isolated from a patient with ABU demonstrated an ability to out-compete uropathogenic *E. coli* in human urine, suggesting an adaptational advantage.¹¹ These alterations to the *E. coli* strain might suggest an evolution of the organism to better adapt to long-term survival in a human host.¹¹

The host response to ABU is also altered compared with symptomatic UTI. Interleukins (IL) 6 and 8 are important pro-inflammatory proteins expressed in response to an infection. In a study from the late 1990s, 63% and 76% of children younger than age 6 with febrile UTI had elevated urine IL-6 and IL-8 levels, respectively. In the same study, no children with ABU had elevated urine IL-6 levels and only 30% had elevated urine IL-8 levels.¹² Recently, there has been an interest in the role of toll-like receptor (TLR) 4, a transmembrane protein important in cellular signaling and activation of the innate immune system, in susceptibility to UTI. Although there are multiple TLRs involved in bacterial recognition, TLR-4 has been widely studied in the context of UTI owing to its location on renal and bladder epithelial cells.¹³ A study in patients 1 to 20 years old showed that TLR-4 expression is reduced by nearly 50% in children with ABU in comparison with patients with symptomatic UTI, which might contribute to the weak mucosal immune response to bacteria in ABU.¹⁴ Subsequent analysis of the TLR-4 promoter sequence has shown fewer genotype variants and reduced expression in ABU patients when compared with patients with symptomatic UTI, further supporting the alterations in TLR-4 at a genomic level in ABU.¹⁵

The combination of altered bacterial characteristics and host response in ABU suggests that the phenomenon might represent a form of commensalism, a symbiotic relationship in which the bacteria benefit and the human host typically derives neither benefit nor harm. In fact, intravesical inoculations with a modified strain of *E coli* isolated from patients with ABU have been used to treat recurrent UTI in the adult population with some success.¹⁶

To treat or not to treat

In the late 1950s and early 1960s, seminal work was done by Kass in the evaluation of antibiotic treatment of ABU in pregnant women, resulting in reduced incidence of pyelonephritis. The results were extrapolated to the general population without appropriate clinical studies, resulting in widespread antibiotic treatment of ABU.^{17,18} Subsequent studies in different populations suggest harm rather than benefit from the treatment of ABU, including in children.

Asymptomatic bacteriuria resolves spontaneously over time in most cases. A 6-year follow-up study of 50 infants who were incidentally found to have ABU when screened using suprapubic aspirates (out of 3581 infants arbitrarily selected to determine the benefit of urine screening in infancy) showed that without treatment, 72% had resolution of the infection and 20% had 1 episode of asymptomatic recurrence.¹⁹ Two of the infants developed pyelonephritis within 2 weeks of screening, but none had evidence of renal damage after a 32-month follow-up. A follow-up report suggested a median ABU persistence of 1.5 months in boys and 2 months in girls.²⁰ A retrospective analysis of urine samples obtained from 54 girls aged 3.3 to 15.5 years who were found to have persistent ABU during a school screening program or on follow-up after UTI showed a median ABU persistence of 2.5 years. However, during that time there was no statistically significant change to bacterial strains isolated, which is thought to be required for development of a symptomatic infection.²¹

Furthermore, even without spontaneous resolution, treatment is often not beneficial. A 4-year follow-up of 63 Scottish girls aged 5 to 7 who were found to have ABU on clean-voided urine samples during a school screening program revealed that there was no significant difference in the development of symptomatic infection or permanent renal damage found among those treated with antibiotics versus placebo.²² Similar results were found in a 3-year follow-up of 116 Swedish girls aged 7 to 15 with ABU.²³

Finally, the treatment of ABU might pose some risk. An outpatient study of 51 German girls younger than age 15 who were found to have ABU on 2 consecutive urine cultures and were treated with antibiotics for an unrelated infection demonstrated that 15% of the girls subsequently suffered an infection with a different bacterial strain, resulting in a symptomatic UTI.²⁴

Specific populations

In the unique population of children who have received renal transplants or who are undergoing invasive procedures involving the urogenital tract, treatment of ABU should be considered. Bacteriuria is common after renal transplant, affecting nearly half of transplant recipients within the first year. A retrospective analysis in 276 adult transplant recipients reported a statistically significant decrease in symptomatic UTI with antibiotic treatment of ABU.²⁵ A study of 142 pediatric renal transplant recipients with a mean age of 9 years showed that 48% had evidence of bacteriuria within the first year after transplantation.²⁶ Of the 66 children with ABU, 18% subsequently became symptomatic without treatment and 81% had a transient rise in plasma creatinine concentration; however, the overall glomerular filtration rate was largely unaffected. Children undergoing invasive procedures involving the urogenital tract might also benefit from treatment. The European Association of Urology recommends antibiotic treatment of ABU before urologic procedures owing to the risk of a tear in the mucosa and potential dissemination of bacteria.²⁷

Conclusion

Recent advances in research support considering ABU a separate entity from symptomatic UTI. Furthermore, in contrast to historical recommendations, recent evidence demonstrates there is minimal benefit and potential harm associated with the treatment of ABU. The current recommendation is not to treat ABU in the pediatric population, with the exception of renal transplant recipients and children undergoing urologic procedures. 🌿

Competing interests

None declared

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